

## PATENT COOPERATION TREATY

## PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY  
(Chapter II of the Patent Cooperation Treaty)

## (PCT Article 36 and Rule 70)

Applicant's or agent's file reference 15656-5PCT	<b>FOR FURTHER ACTION</b>	
See Form PCT/IPEA/416		
International application No. PCT/CA2004/000011	International filing date (day/month/year) 05.01.2004	Priority date (day/month/year) 06.01.2003
International Patent Classification (IPC) or national classification and IPC A61K47/48, A61P25/00		
Applicant TRANSFERT PLUS et al		
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 12 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> <i>(sent to the applicant and to the International Bureau) a total of 13 sheets, as follows:</i></p> <p><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> <i>(sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</i></p>		
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input checked="" type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input checked="" type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>		
Date of submission of the demand 22.07.2004	Date of completion of this report 01.06.2005	
Name and mailing address of the international preliminary examining authority:   European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer  Gonzalez Ramon, N Telephone No. +31 70 340-3466	

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**Box No. I Basis of the report**

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
  - This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
    - international search (under Rules 12.3 and 23.1(b))
    - publication of the international application (under Rule 12.4)
    - international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements\*** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

**Description, Pages**

1-37 as originally filed

**Claims, Numbers**

1-96 received on 04.05.2005 with letter of 04.05.2005

**Drawings, Sheets**

1/20-20/20 as originally filed

- a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3.  The amendments have resulted in the cancellation of:
  - the description, pages
  - the claims, Nos. 97-102
  - the drawings, sheets/figs
  - the sequence listing (*specify*):
  - any table(s) related to sequence listing (*specify*):
4.  This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
  - the description, pages
  - the claims, Nos.
  - the drawings, sheets/figs
  - the sequence listing (*specify*):
  - any table(s) related to sequence listing (*specify*):

\* If item 4 applies, some or all of these sheets may be marked "superseded."

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**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

the entire international application,

claims Nos. 1-4,6-20,22-36,38-50,52-63,65-71,74-96 partially; 5,21,37,51,64,73 complete because:

the said international application, or the said claims Nos. 85-96 in relation to industrial applicability, see separate sheet relate to the following subject matter which does not require an international preliminary examination (specify):

**see separate sheet**

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-4,6-20,22-36,38-50,52-63,65-72,74-96 partially; see separate sheet are so unclear that no meaningful opinion could be formed (*specify*):

**see separate sheet**

the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

no international search report has been established for the said claims Nos. 1-4,6-20,22-36,38-50,52-63,65-71,74-96 partially; 5,21,37,51,64,73 complete

the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form  has not been furnished  
 does not comply with the standard

the computer readable form  has not been furnished  
 does not comply with the standard

the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

See separate sheet for further details

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**Box No. IV Lack of unity of invention**

1.  In response to the invitation to restrict or pay additional fees, the applicant has:
  - restricted the claims.
  - paid additional fees.
  - paid additional fees under protest.
  - neither restricted nor paid additional fees.
2.  This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
  - complied with.
  - not complied with for the following reasons:  
**see separate sheet**
4. Consequently, this report has been established in respect of the following parts of the international application:
  - all parts.
  - the parts relating to claims Nos. 4, 20, 36, 50, 63 complete; 1-3, 6-19, 22-35, 38-49, 52-62, 65-72, 74-96 partially .

**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	4,20,36,40-42,47-50, 52-58,60-63, 65-70, 86, 87, 89-96
	No: Claims	1-3,6-19,22-35,38,39,43-46,59, 71, 72, 74-85, 88
Inventive step (IS)	Yes: Claims	1-4, 6-20, 22-36, 38-50, 52-63, 65-72, 74-96
Industrial applicability (IA)	Yes: Claims	1-4, 6-20, 22-36, 38-50, 52-63, 65-72, 74-84
	No: Claims	85-96

2. Citations and explanations (Rule 70.7):

**see separate sheet**

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**Box No. VI Certain documents cited**

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

**Supplemental Box relating to Sequence Listing**

**Continuation of Box I, item 2:**

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

a. type of material:

a sequence listing  
 table(s) related to the sequence listing

b. format of material:

in written format  
 in computer readable form

c. time of filing/furnishing:

contained in the international application as filed  
 filed together with the international application in computer readable form  
 furnished subsequently to this Authority for the purposes of search and/or examination  
 received by this Authority as an amendment on

2.  In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

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**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 85-96 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Claims 1-4, 6-20, 22-36, 38-50, 52-63, 65-72, 74-96 as far as related to the first invention encompass a genus of compounds defined only by their function, namely: "a functional derivative" (claims 1, 17, 33, 47, 60, 71); "transporting does not affect blood brain barrier integrity" (claims 2, 18, 34, 48, 61, 72); "transporting effected by receptor mediated transcytosis or adsorptive mediated transcytosis" (claims 7, 23, 39, 53, 66, 75); "agent is releasable form said carrier after transport across the blood brain barrier" (claims 12, 28, 44, 57, 68, 80); "agent is released from said carrier after transport across the blood brain barrier" (claims 13, 29, 45, 58, 69, 81), wherein the relationship between the structural features of the members of the genus and said function have not been defined.

In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition.

The fact that one could have assayed a compound of interest using the described assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (**other than those that might be particularly disclosed in an application**) would fall within the scope of what is claimed.

It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity.

Moreover said definitions such as functional derivative would encompass not yet described compounds and would therefore contravene Art. 5. PCT.

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Therefore, claims 1-4, 6-20, 22-36, 38-50, 52-63, 65-72, 74-96 do not fulfil the requirements of Art. 5 and Art. 6 PCT.

Moreover present claims 1-4, 6-20, 22-36, 38-50, 52-63, 65-72, 74-96 relate to compounds defined by reference to vague characteristics, namely: "a drug", "a medicine", "an anticancer agent", "a molecule active at the level of the central nervous system" (claims 3, 19, 35, 49, 62, 71); "agent has a maximum molecular weight of 160,000 Daltons" (claims 6, 22, 38, 52, 65, 74)

Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed.

Furthermore claims 17-20, 22-32, 71, 72, 74-96 are not supported by the description (Art. 5 PCT).

No support is to be found throughout the application document as filed disclosing the claimed conjugates wherein the agent is an anti-cancer agent, in particular paclitaxel neither the use of the said conjugates as claimed.

The only effective disclosure showing conjugates (description pages 27-30) describe <sup>125I</sup>-aprotinin and aprotinin-biotin conjugates, not encompassed under the said denomination of **anticancer agent** conjugate as claimed.

A mere generic enumeration of anticancer agent and not the particular paclitaxel as part of the therapeutic agent is done regardless of its forming part of a conjugate construct (page 15, paragraph 2) and therefore cannot be considered as sufficient disclosure for the skilled person in order to perform the invention in its whole scope (Ar. 5 PCT).

Support with regard to the first invention is only to be found in the present application for those parts relating to the compounds explicitly disclosed in the examples and those specifically mentioned by chemical name in claims 1, 18, 33, 36, 47, 50, 60, 63, 71 excluding the vague term "functional derivative" .

No international Preliminary Examination will be carried out in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT).

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**Re Item IV**

**Lack of unity of invention**

The Examining Division agrees with the objection put forward by the Search Division as to lack of unity (Rule 13 PCT), the reasons for the objection as stated in the international search report.

The present application lacks unity of invention, containing the following subjects as identified by the ISA:

1. Claims: 4, 20, 36, 50, 63 complete; 1-3, 6-19, 22-35, 38-49, 52-62, 65-72, 74-96 partially

Carrier for transporting an agent attached thereto across the blood brain barrier wherein the agent is anticancer agent paclitaxel, said carrier being selected from the group consisting of aprotinin, a functional derivative of aprotinin, Angio-pep1 and a functional derivative of Angio-pep1. Conjugate comprising the carrier and paclitaxel, pharmaceutical composition and use of the same for neurological disease (brain tumour, brain metastasis, schizophrenia, epilepsy, Alzheimer's disease, Parkinson's disease, Huntington's disease, stroke and obesity).

2. Claims: 1-3, 5-19, 21-35, 37-49, 51-62, 64-96 partially

Carrier for transporting an agent attached thereto across the blood brain barrier wherein the agent is a radioactive label, said carrier being selected from the group consisting of aprotinin, a functional derivative of aprotinin, Angio-pep1 and a functional derivative of Angio-pep1. Conjugate comprising the carrier and radioactive label, pharmaceutical composition and use of the same for neurological disease (brain tumour, brain metastasis, schizophrenia, epilepsy, Alzheimer's disease, Parkinson's disease, Huntington's disease, stroke and obesity)

3. Claims: 1-3, 5-19, 21-35, 37-49, 51-62, 64-96 partially

Carrier for transporting an agent attached thereto across the blood brain barrier wherein the agent is a green fluorescent protein, a histag protein, and beta galactosidase, said

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carrier being selected from the group consisting of aprotinin, a functional derivative of aprotinin, Angio-pep1 and a functional derivative of Angio-pep1. Conjugate comprising the carrier and the protein agent, pharmaceutical composition and use of the same for neurological disease (brain tumour, brain metastasis, schizophrenia, epilepsy, Alzheimer's disease, Parkinson's disease, Huntington's disease, stroke and obesity)

**An international search report has only been established for the subject matter of invention 1 as listed above.**

The applicant was informed that the search is the responsibility of the ISA under Chapter I of the PCT, the procedure before the ISA is closed and that there is no provision in the PCT for a review of or an appeal against the findings of the ISA, either by the ISA itself or by the IPEA.

No international Preliminary Examination will be carried out in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT) (i. e. inventions 2, 3 as listed above)

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

For the assessment of the present claims 85-96 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The applicant's attention is drawn to the fact that the present opinion expressed as to novelty, inventive step and industrial applicability refers only to matter for which an international search report has been drawn up.

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No international Preliminary Examination will be carried out in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT)

Reference is made to the following documents:

- D1: DE 199 53 696 A (CHERKASKY ALEXANDER) 10 May 2001
- D2: SHIMURA T ET AL: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 258, no. 2, 1991, pages 459-465.
- D3: DEMEULE M ET AL: JOURNAL OF NEUROCHEMISTRY, vol. 83, no. 4, November 2002, pages 924-933.
- D4: SEIDEL G ET AL: NAUNYN-SCHMIEDEBERG'S ARCHIVES OF PHARMACOLOGY, vol. 284, no. 4, 1974, page R73.
- D5: MARTEL ET AL: STP PHARMA SCIENCES, PARIS, FR, vol. 7, no. 1, 1997, pages 28-36.

**Novelty Article 33(2) PCT**

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-3, 6-19, 22-35, 38, 39, 43-46, 59, 71, 72, 74-85, 88 is not new in the sense of Article 33(2) PCT.

D1 discloses Beta-amyloid A4 (homologue of claimed Angio-pep1 according to present application figure 17; description page 32-33 and embraced consequently as **functional derivative of Angio-pep1 as claimed**) linked to a synzyme. Optionally conjugated to another molecule (see claim 3, fig. 1). The construct is capable for crossing the blood brain barrier (see col. 1 lines 15-32).

Consequently the subject matter of claims 1-3, 6-19, 22-35, 38, 39, 43-46, 59, 71, 72, 74-85, 88 is not new over D1.

**Inventive step Article 33(3) PCT**

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-4, 6-20, 22-36, 38-50, 52-63, 65-72, 74-96 does not involve an inventive step in the sense of Article 33(3) PCT.

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The problem underlying the present application is the delivery of drugs across the blood-brain barrier for treating disorders of the central nervous system (see page 1, second paragraph).

As solution to this problem a composition comprising a carrier wherein aprotinin and Angio-pep1 linked to an anticancer agent, in particular paclitaxel is proposed as the first invention.

Document D3, which can be considered the closest prior art, already addresses the problem of delivery of drugs across the blood brain barrier with the use of P97 (melanotransferrin) as delivery system to target drugs, peptides or enzymes directly to the brain (see abstract, discussion).

The difference between D3 and the subject matter of present claims 1-4, 6-20, 22-36, 38-50, 52-63, 65-72, 74-96 is the fact that the particular conjugate of aprotinin or Angio-pep1 with an anticancer agent (as paclitaxel) neither the use for the specific treatment of neurological diseases consisting on brain tumour, brain metastasis, schizophrenia, epilepsy, Alzheimer, Parkinson, Huntington, stroke, blood brain barrier related malfunction disease, obesity are explicitly disclosed in D3.

Nevertheless, D1 renders obvious the use of a beta-amyloid A4 homologue as the claimed Angio-pep1 conjugated to another molecule as such construct is capable for crossing the blood brain barrier (see col. 1 lines 15-32; claim 3).

The use of aprotinin is also rendered obvious to the skilled person in view of the teaching of D4, where the effect of **trasylo1** (namely aprotinin) in increasing the brain concentration of drug harmine by affecting on the permeability of the blood brain barrier is described (see abstract).

Furthermore the attention of the applicant is drawn to the fact that all embodiments covered by the claims should satisfy the criteria of inventive step. When the inventive step is solely based on the achievement of a technical effect, such as "transporting of an agent across the blood brain barrier", substantially all embodiments of independent claim 1 should exhibit this effect.

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It should be credible that all the alternatives encompassed by the claims are a solution to the problem.

However, it is evident that the number of compounds encompassed under: "a functional derivative" (claims 1, 17, 33, 47, 60, 71); "a drug", "a medicine", "an anticancer agent", "a molecule active at the level of the central nervous system" (claims 3, 19, 35, 49, 62, 71); "agent has a maximum molecular weight of 160,000 Daltons" (claims 6, 22, 38, 52, 65, 74); "an agent attached to said carrier" (claim 17) is such that it is unlikely that all of them posses the effect claimed.

Therefore, as part of the subject matter of claims 1-4, 6-20, 22-36, 38-50, 52-63, 65-72, 74-96 is unlikely to exhibit this particular technical effect in a credible manner, said subject matter cannot involve inventive step.

**Re Item VI**

**Certain documents cited**

**Certain published documents**

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO03009815	06/02/2003	25/07/2002	25/07/2001

This earlier application shows:

LRP (low density lipoprotein related) receptor ligands embracing aprotinin and P97 (see page 4, line 6) with functional effect on transcytosis (see fig 17; claim 25).

Conjugates of the same with therapeutic active agents including paclitaxel (see page 37, line 8).

Uses of the same for the treatment of neurological disorders are also described (see claim 8).

Thus, it would be prejudicial to the novelty of the subject-matter of claims 1-4, 6-20, 22-36, 38-50, 52-63, 65-72, 74-96 of the present application.